

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

SE 90/756

REC 27 JUN 2000

Intyg Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) Sökande Astra AB, Södertälje SE
Applicant (s)

(21) Patentansökningsnummer 9904419-0
Patent application number

(86) Ingivningsdatum 1999-12-03
Date of filing

Stockholm, 2000-06-21

För Patent- och registreringsverket
For the Patent- and Registration Office


Görel Gustafsson

Avgift
Fee

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT- OCH
REGISTRERINGSVERKET
SWEDEN

Postadress/Address
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 866 02 86
08-866 02 86

NEW USE**Field of the Invention**

- 5 This invention relates to a new use of low molecular weight thrombin inhibitors.

Background and Prior Art

- 10 Blood coagulation is the key process involved in both haemostasis (i.e. the prevention of blood loss from a damaged vessel) and thrombosis (i.e. the formation of a blood clot in a blood vessel, sometimes leading to vessel obstruction).
- 15 Coagulation is the result of a complex series of enzymatic reactions. One of the ultimate steps in this series of reactions is the conversion of the proenzyme prothrombin to the active enzyme thrombin.

- Thrombin is known to play a central role in coagulation. It activates
- 20 platelets, leading to platelet aggregation, converts fibrinogen into fibrin monomers, which polymerise spontaneously into fibrin polymers, and activates factor XIII, which in turn crosslinks the polymers to form insoluble fibrin. Furthermore, thrombin activates factor V and factor VIII leading to a "positive feedback" generation of thrombin from
- 25 prothrombin.

Effective inhibitors of thrombin are thus known, and/or are expected, to be useful as anticoagulants and therefore useful in the therapeutic treatment of thrombosis and related disorders.

- 5 The early development of low molecular weight inhibitors of thrombin has been described by Claesson in Blood Coagul. Fibrinol. (1994) 5, 411. Low molecular weight thrombin inhibitors have been described more recently in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336,
10 WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422 and WO 98/57932; and European Patent Applications 648
15 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596.

In particular, international patent application WO 94/29336 discloses a
20 group of compounds, including $\text{HOOC-CH}_2\text{-(R)Cgl-Aze-Pab-H}$, which is also known as melagatran (see Example 1 of WO 94/29336, and the list of abbreviations in this document). International Patent Application WO 97/23499 discloses prodrugs of *inter alia* melagatran.

- 25 None of the above-mentioned documents disclose or suggest the administration of an active thrombin inhibitor in conjunction with a prodrug of that thrombin inhibitor, or indeed in conjunction with a prodrug of any thrombin inhibitor.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are major health problems, which may give rise to serious outcomes. In particular, PE may be fatal, or may result in the development of pulmonary hypertension and heart failure from recurrent embolism. DVT may result in post-thrombotic venous insufficiency and ulcers in the affected part of the body (e.g. leg). Both are common conditions, which have a great impact on worldwide healthcare costs.

There is a considerable incidence of DVT and PE following orthopaedic surgery. For example, in patients undergoing total hip replacement, the incidence of DVT in the absence of thromboprophylaxis may be as high as 45 to 57%. Further, the incidence of proximal DVT may be between 23 and 36%, and that of fatal PE, 0.34 to 6%. In patients undergoing total knee replacement in the absence of thromboprophylaxis, the postoperative incidence of DVT is between 40 and 84%, of proximal DVT is between 9 and 20%, and of fatal PE is between 0.2 and 0.7%. In patients undergoing general surgery in the absence of thromboprophylaxis, the postoperative incidence of DVT is about 25%. (Reference: Chest (1998) 114, 531S to 560S.)

20

Low-dose, subcutaneous (s.c.) unfractionated heparin is the most widely used current prophylactic treatment for venous thromboembolism resulting from orthopaedic and general surgery. The incidence of DVT after total hip replacement has been shown to be reduced (see Chest reference above).

25

The use of low-molecular weight heparin (LMWH) in the prophylaxis of DVT following total hip and knee replacement operations has been shown to further the reduce incidence (when compared to low dose unfractionated

heparin), without a concomitant increase in bleeding (see Chest reference above).

However, prolonged treatment with heparins has been shown to give rise
5 to an increased risk of osteoporosis. Heparins may also give rise to
"heparin-induced thrombocytopenia" (HIT), are dependent on the plasma
level of the endogenous thrombin inhibitor, antithrombin, and do not
inactivate clot-bound thrombin.

10 Oral anticoagulants, such as warfarin (a vitamin K antagonist), has also
been shown to be effective in reducing DVT after major surgery (see
Chest reference above). However, due to the risk of bleeding, and the
need for frequent laboratory control, the use of this substance is generally
reserved for high risk patients, and/or for long term use. Vitamin K
15 antagonists also demonstrate a notable risk of interaction with other drugs
and certain foods, and their use requires monitoring of the patient's blood
coagulation status.

Antiplatelet agents, such as aspirin, have been shown to have limited
20 efficacy in preventing DVT (see Chest reference above).

Comparative clinical studies carried out during the course of total hip
replacement operations have shown that subcutaneous administration of
the thrombin inhibitor hirudin is superior to unfractionated heparin and
25 LMWH in reducing the frequency of total and proximal DVT with no
corresponding increase in bleeding (see Eriksson *et al* in Lancet, 347, 635
(1996) and J. Bone Joint. Surg., Sep., 11 (1996)). However, hirudin is
expensive and has an immunogenic potential.

Thus, there is a need for effective treatments of thrombotic conditions such as DVT.

Disclosure of the Invention

5

We have found, surprisingly, that administration of a low molecular weight thrombin inhibitor in conjunction with a prodrug of a (or a prodrug of that) thrombin inhibitor gives rise to a notable anticoagulant effect.

10 According to a first aspect of the invention there is provided a kit of parts comprising:

(a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

15

(b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

20 which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

It is preferred that the prodrug of component (b) is a prodrug of the active low molecular weight thrombin inhibitor of component (a).

25

According to a further aspect of the invention, there is provided a method of making a kit of parts as defined herein, which method comprises bringing a component (a), as defined above, into association with a

component (b), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components "into association with" each other, we
5 include that components (a) and (b) may be:

- (i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
- (ii) packaged and presented together as separate components of a
10 "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

- (1) one of components (a) and (b) as defined herein; together with
- 15 (2) instructions to use that component in conjunction with the other of the two components.

The kits of parts defined herein may comprise more than one formulation including an appropriate quantity/dose of thrombin inhibitor, and/or more
20 than one formulation including an appropriate quantity/dose of respective prodrug, in order to provide for repeat dosing. If more than one formulation (comprising thrombin inhibitor or prodrug) is present, such formulations may be the same, or may be different in terms of the dose of thrombin inhibitor/prodrug, chemical composition and/or physical form.

25

A further aspect of the invention provides a method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with
- 5 (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
- to a patient suffering from, or susceptible to, such a condition.

10

For the avoidance of doubt, as used herein, the term "treatment" includes therapeutic and/or prophylactic treatment.

"Pharmaceutically acceptable derivatives" of thrombin inhibitors and

15 prodrugs includes salts (e.g. pharmaceutically acceptable non-toxic organic or inorganic acid addition salts) and solvates.

By "administration in conjunction with", we include that respective formulations comprising thrombin inhibitor and/or prodrug are

20 administered, sequentially, separately and/or simultaneously, over the course of treatment of the relevant condition, which condition may be acute or chronic. Preferably, the term includes that the two formulations are administered (optionally repeatedly) sufficiently closely in time for there to be a beneficial effect for the patient, that is greater, over the

25 course of the treatment of the relevant condition, than if either of the two formulations are administered (optionally repeatedly) alone, in the absence of the other formulation, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular

condition, will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

Thus, the term "in conjunction with" includes that one or other of the two
5 formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration with the other component. When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of thrombin inhibitor and prodrug are administered within 48 hours (e.g. 24
10 hours) of each other.

Components (a) and (b) as described herein may also be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including low molecular thrombin inhibitor and prodrug).

15

Thus, there is further provided a pharmaceutical formulation including a low molecular weight thrombin inhibitor (or a pharmaceutically acceptable derivative thereof) and a prodrug of a low molecular weight thrombin inhibitor (or a pharmaceutically acceptable derivative of that prodrug), in
20 admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

The term "low molecular weight thrombin inhibitor" will be understood by those skilled in the art. The term may also be understood to include any composition of matter (e.g. chemical compound) which inhibits
25 thrombin to an experimentally determinable degree in *in vivo* and/or in *in vitro* tests, and which possesses a molecular weight of below 2,000, preferably below 1,000.

Preferred low molecular weight thrombin inhibitors include low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors.

5 The term "low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors" will be well understood by one skilled in the art to include low molecular weight thrombin inhibitors with one to four peptide linkages, and includes those described in the review paper by Claesson in Blood Coagul. Fibrin. (1994) 5, 411, as well as those
10 disclosed in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO
15 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422 and WO 98/57932; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the disclosures in all of which documents are hereby incorporated by
20 reference.

Preferred low molecular weight peptide-based thrombin inhibitors include HOOC-CH₂-(R)Cha-Pic-Nag-H (known as inogatran; see International Patent Application WO 93/11152 and the list of abbreviations therein) and,
25 especially, HOOC-CH₂-(R)Cgl-Aze-Pab-H (known as melagatran; see International Patent Application WO 94/29336 and the list of abbreviations therein).

The term "prodrug" of a low molecular weight thrombin inhibitor includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form a low molecular weight thrombin inhibitor (as defined herein), in an experimentally-detectable amount, and within a
5 predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)), following oral or parenteral administration. Prodrugs of the thrombin inhibitor melagatran that may be mentioned include those disclosed in international patent application WO 97/23499. Preferred prodrugs are those of the formula $R^1O_2C-CH_2-$
10 $(R)Cgl-Aze-Pab-OH$ (see the list of abbreviations in WO 97/23499), wherein R^1 represents linear or branched C_{1-6} alkyl (e.g. C_{1-4} alkyl, especially methyl, propyl and, particularly, ethyl) and the OH group replaces one of the amidino hydrogens in Pab.

15 The term "condition in which inhibition of thrombin is required or desired" will be understood by those skilled in the art to include the following:

The treatment and/or prophylaxis of thrombosis and hypercoagulability in
20 blood and tissues of animals including man. It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include inherited or acquired activated protein C resistance, such as the factor V-mutation (factor V Leiden), and inherited
25 or acquired deficiencies in antithrombin III, protein C, protein S, heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulating antiphospholipid antibodies (Lupus anticoagulant), homocysteinemi, heparin induced thrombocytopenia and defects in fibrinolysis.

The treatment of conditions where there is an undesirable excess of thrombin without signs of hypercoagulability, for example in neurodegenerative diseases such as Alzheimer's disease.

5

Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis (e.g. DVT) and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial
10 thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction, or caused by congestive heart failure; prophylaxis of re-occlusion (ie thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of re-
15 thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; anticoagulant treatment
20 when blood is in contact with foreign surfaces in the body such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; and anticoagulant treatment when blood is in contact with medical devices outside the body such as during cardiovascular surgery using a heart-lung machine or in
25 haemodialysis; the therapeutic and/or prophylactic treatment of idiopathic and adult respiratory distress syndrome, pulmonary fibrosis following treatment with radiation or chemotherapy, septic shock, septicemia, inflammatory responses, which include, but are not limited to, edema, acute or chronic atherosclerosis such as coronary arterial disease, cerebral

arterial disease, peripheral arterial disease, reperfusion damage, and restenosis after percutaneous trans-luminal angioplasty (PTA).

Preferred conditions include thrombosis, especially DVT, including distal
5 and proximal DVT. The present invention finds particular utility in the prophylactic treatment of DVT resulting from surgery, such as gastrointestinal, or orthopaedic, surgery (e.g. hip or knee replacement). This includes DVT resulting from immobilisation after surgery.

10 In accordance with the invention, thrombin inhibitors, prodrugs of thrombin inhibitors, and derivatives of either, may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the
15 thrombin inhibitor or prodrug in a pharmaceutically acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.

20 Preferred modes of delivery are systemic. For melagatran and derivatives thereof, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran, preferred modes of administration are oral.

25 In the therapeutic treatment of mammals, and especially humans, thrombin inhibitors, prodrugs of thrombin inhibitors, and derivatives of either, may be administered alone, but will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due

regard to the intended route of administration and standard pharmaceutical practice.

Suitable formulations for use in administering thrombin inhibitors are
5 known in the art, and include those known from US Patent N° 4,346,078;
International Patent Applications WO 93/11152, WO 93/18060, WO
93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609,
WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO
96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708,
10 WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO
97/11693, WO 97/24135, WO 97/47299, WO 98/01422 and WO
98/57932; and European Patent Applications 648 780, 468 231, 559 046,
641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530
167, 293 881, 686 642, 669 317, 601 459 and 623 596, the disclosures in
15 all of which documents are hereby incorporated by reference.

Suitable formulations for use with melagatran, derivatives and prodrugs
thereof are described in the literature, for example as described in *inter*
alia international patent applications WO 94/29336, WO 96/14084, WO
20 96/16671, WO 97/23499, WO 97/39770, WO 97/45138 and WO
98/16252, the disclosures in which documents are hereby incorporated by
reference. Otherwise, the preparation of suitable formulations may be
achieved non-inventively by the skilled person using routine techniques.

25 The amounts of thrombin inhibitor, prodrug, or derivative of either, in the
formulation will depend on the severity of the condition, and on the
patient, to be treated, as well as the compound(s) which is/are employed,
but may be determined non-inventively by the skilled person.

Suitable doses of thrombin inhibitors, prodrugs and derivatives of either, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the
 5 prior art documents disclosing thrombin inhibitors that are mentioned hereinbefore, the disclosures in which are incorporated by reference.

In the case of melagatran, suitable doses of active compound, prodrugs and derivatives thereof, in the therapeutic and/or prophylactic treatment of
 10 mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 $\mu\text{mol/L}$, for example in the range 0.001 to 5 $\mu\text{mol/L}$ over the course of treatment of the relevant condition.

In any event, the physician, or the skilled person, will be able to
 15 determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage
 20 ranges are merited, and such are within the scope of this invention.

The sequence in which the formulations comprising thrombin inhibitor, and prodrug, may be administered (i.e. whether, and at what point, sequential, separate and/or simultaneous administration takes place) may
 25 be determined by the physician or skilled person. For example, the sequence may depend upon many factors that will be evident to the skilled person, such as whether, at any time during the course or period of treatment, one or other of the formulations cannot be administered to the patient for practical reasons (e.g. the patient is unconscious and thus

unable to take an oral formulation comprising either thrombin inhibitor or prodrug).

For example, in the treatment of thrombosis (e.g. DVT) resulting from surgery, such as gastrointestinal, or orthopaedic, surgery, and when the active thrombin inhibitor is melagatran, it is preferred that the formulation comprising melagatran is administered parenterally within two days (e.g. within 24 hours) of surgery (either prior to or after surgery), and particularly immediately prior to (e.g. within 2 hours), and/or within up to 12 hours after surgery (e.g. at least one hour after surgery), and thereafter for up to between 3 and 7 (e.g. between 0 and 2, such as between 1 and 2) days after that surgery, and that the formulation comprising prodrug is administered orally within 7 days following that surgery (preferably once administration of melagatran has been terminated) for up to e.g. between 11 and 40 days, preferably 9 days, more preferably up to 8 days.

The method described herein may have the advantage that, in the treatment of conditions in which inhibition of thrombin is required or desired, it may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it may have other useful pharmacological properties over, similar methods known in the prior art for the treatment of such conditions.

The invention is illustrated, but in no way limited, by the following example.

Example 1Clinical Trial - Melagatran and EtOOC-CH₂-(R)Cgl-Aze-Pab-OH
Combination Therapy

- 5 A controlled, randomised, parallel group, Swedish multi-centre pilot study was carried out. The study was open with regard to the drugs under evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the experiments with regard to the doses of melagatran and the prodrug of melagatran, EtOOC-CH₂-(R)Cgl-Aze-Pab-
- 10 OH (P; see WO 97/23499).

Dalteparin (Fragmin®; Pharmacia-Upjohn) was used as a reference compound.

- 15 Patients scheduled for primary elective total hip or knee replacement were eligible for inclusion, and were randomly selected into one of three groups, each to receive different doses of melagatran and P, or dalteparin. In all, 135 patients were included in the study, of which 105 patients could be used for evaluation with respect to thromboembolic events using central
- 20 assessment of locally performed phlebograms.

- About 32 patients in each treatment group were evaluated according to the protocol. A stratified randomisation, by centre and type of surgery, was used to ensure that approximately equal numbers of patients were given
- 25 each of the drugs under evaluation at all participating centres (in all six centres were used) for both types of surgery (hip or knee). Each centre received study drugs in blocks of four, separately for hips and knees. Within each block, the order of the study drugs was randomised.

The following formulations were used in the study:

Melagatran - 5, 10 or 20 mg/mL in aqueous saline solution.

- 5 P - appropriate weight (see below) in a tablet also comprising 59 to 63 mg corn starch, 115 mg microcrystalline cellulose and 2 mg sodium stearyl fumarate.

The following doses of melagatran and P were used in the study:

10

Treatment A - s.c. melagatran (1 mg) b.i.d. for 2 days, followed by oral administration of P (6 mg) b.i.d. for 6 to 9 days.

- 15 Treatment B - s.c. melagatran (2 mg) b.i.d. for 2 days, followed by an oral administration of P (12 mg) b.i.d. for 6 to 9 days.

Treatment C - s.c. melagatran (4 mg) b.i.d. for 2 days, followed by an oral administration of P (24 mg) b.i.d. for 6 to 9 days.

- 20 The patients receiving melagatran and P received treatment on the day of surgery. The patient received the first injection after induction of anaesthesia immediately before surgery. For knee-patients, the pre-operative melagatran injection was given before tourniquets were applied. The second injection was given in the evening the same day. The patient
25 received one melagatran injection in the morning and one in the evening over the next 24 hours, until oral administration of P, twice daily, started. The first oral dose of P was always taken in the morning. Thus, the total treatment period comprised was between 8 and 11 days.

Treatment D - dalteparin (Fragmin®): one s.c. injection of 5000 U during the evening of the day before surgery, continuing with one s.c. injection every evening over a treatment period of 8 to 11 days.

- 5 The plasma concentrations of melagatran were recorded.

The results of the trial, in terms of the frequencies of thromboembolism after hip or knee surgery, are tabulated below:

| | Treatment A | | Treatment B | | Treatment C | | Treatment D | |
|---------|-------------|-----|-------------|-----|-------------|-----|-------------|-----|
| | (n) | (%) | (n) | (%) | (n) | (%) | (n) | (%) |
| Outcome | 6/29 | 21 | 6/24 | 25 | 4/24 | 16 | 5/27 | 19 |

10

These data show that a combination of subcutaneously administered melagatran and orally administered P is effective in preventing DVT after orthopaedic surgery.

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138

Claims

1. A kit of parts comprising:

- 5 (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
- (b) a pharmaceutical formulation including a prodrug of a low
10 molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

15

2. A kit of parts as claimed in Claim 1, wherein the prodrug of component (b) is a prodrug of the thrombin inhibitor of component (a).

3. A kit of parts as claimed in Claim 1 or Claim 2, wherein components
20 (a) and (b) are suitable for sequential, separate and/or simultaneous use in the treatment of a condition in which inhibition of thrombin is required or desired.

4. A kit of parts as claimed in Claim 3, wherein the condition is deep
25 venous thrombosis.

5. A kit of parts as claimed in any one of Claims 1 to 4, wherein the thrombin inhibitor is melagatran.

6. A kit of parts as claimed in Claim 5, wherein the prodrug is of the formula



wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group
5 replaces one of the amidino hydrogens in Pab.

7. A kit of parts as claimed in Claim 6, wherein R^1 represents methyl, ethyl or propyl.

10 8. A kit of parts as claimed in any one of the preceding claims, wherein the formulation comprising thrombin inhibitor, or derivative thereof, is a parenteral formulation and that comprising the prodrug, or derivative thereof, is an oral formulation.

15 9. A method of making a kit of parts as defined in any one of Claims 1 to 8, which method comprises bringing a component (a) according to any one of Claims 1 to 8, into association with a component (b) according to any one of Claims 1 to 8, thus rendering the two components suitable for administration in conjunction with each other.

20

10. A kit of parts comprising:

(1) one of components (a) and (b) as defined in any one of Claims 1 to 8; together with

(2) instructions to use that component in conjunction with the other of the
25 two components.

11. A pharmaceutical formulation including a low molecular weight thrombin inhibitor (or a pharmaceutically acceptable derivative thereof) and a prodrug of a low molecular weight thrombin inhibitor (or a

pharmaceutically acceptable derivative of that prodrug), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with
 - 10 (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
- to a patient suffering from, or susceptible to, such a condition.

15

13. A method as claimed in Claim 12 in which component (a) is administered prior to commencement of administration of component (b).

14. A method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of a formulation as defined in Claim 11 to a patient suffering from, or susceptible to, such a condition.

15. A method as claimed in any one of Claims 12 to 14, wherein the condition is deep venous thrombosis.

16. A method as claimed in Claim 15, wherein the thrombosis results from surgery.

17. A method as claimed in Claim 16, wherein the surgery is gastrointestinal surgery or orthopaedic surgery.

18. A method as claimed in Claim 16 or Claim 17, wherein component

- 5 (a) is administered parenterally prior to and/or after surgery and component (b) is administered orally following that surgery.

19. The use of a thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment
10 or prophylaxis of a condition in which inhibition of thrombin is required or desired, which treatment or prophylaxis comprises administration of:

- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant,
15 diluent or carrier; in conjunction with
- (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
20 to a patient suffering from, or susceptible to, such a condition.

23
ABSTRACT

According to the invention there is provided a kit of parts comprising:

- 5 (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
- 10 (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other, as well as the use of such a kit of parts in the treatment of a condition in which inhibition of

15 thrombin is required or desired.